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Research Paper

Study of Serum Uric Acid, BMR, BP, and Urine Protein Levels in Pre-Eclampsia of Pregnancy.

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ABSTRACT: *The study of serum uric acid(SUA) concentration in the pre-eclamptic pregnant women attending antenatal care in some slated primary health care center in in Obio-Akpor Local Government Area, Rivers State Nigeria was carried out. One hundred(100) pre-eclamptic and normal pregnant cases in their different trimesters of pregnancy were recruited in the study. Serum uric acid(SUA) concentration, urinary protein measurement, Body Mass Index (BMI), Blood Pressure (BP) were determined respectively.The result of the study showed that there was a significantly high SUA concentration differing from 1st to 3rd trimesters in the pre-eclamptic pregnancies than in the normal and comparison made amongst them was statistically significant (P<0.05). Serum uric acid increased in pre-eclamptic pregnant women especially at the third trimester and can be used as a marker for pre-eclampsia.*

I. INTRODUCTION

The word eclampsia is from the Greek term for lightning. The first known description of the condition was by Hippocrates in the 5th century BCE (Emile 2006). Preeclampsia is a disorder of pregnancy characterized by high blood pressure and a large amount of protein in the urine (Eiland*et al.*, 2012). Preeclamptic disorder generally occurs in the third trimester of pregnancy and gets worse over time (Al-Jameil*et al.*, 2014). In severe disease there may be breakdown of red blood cell, a low blood platelet count impaired liver function, kidney dysfunction, swelling, shortness of breath due to accumulation of fluid within the lungs, or visual disturbances (Al-Jameil*et al.*, 2014). The disorder increases the risk of poor outcomes for both the mother and the baby according to a report by the American College Obstetricians and Gynecologists (2013).

The 2013 Global Burden of Disease (GBD) has reported hypertension in pregnancy and its related diseases as one of the most common causes of complications in pregnancy ,accounting for about 29,000 (Sedgh, *et al.*, 2014) Study on family planning for intended and unintended pregnancies worldwide in 2012 reported that about 213 million pregnancies occurred in 2012 ,out of which 190 million were in the developing countries and 23 million in the developed world, resulting to about 133 pregnancies per 1,000 women between the ages of 15 and 44 (Sedgh, *et al.*, 2014). About 10% to 15% of recognized pregnancies end in miscarriage (Joesph*et al.*, 2012). African alone in 2012 had 54 million pregnancies, 120 million occurred in Asia, 19 million in Europe, 18 million in Latin America and the Caribbean, 7 million in North America, and 1 million in Oceania (Sedgh, *et al.*, 2014). Pregnancy rates are 140 per 1000 women of childbearing age in the developing world and 94 per 1000 in the developed world (Sedgh, *et al.*, 2014).

Globally, an estimated 270,000 women die from pregnancy-related diseases and complications each year (Dabas*et al.*, 2015),pre-eclampsia of pregnancy taking the lead .Pre-eclampsia is a serious pregnancy complication characterized by hypertension, proteinuria with or without pathological edema.

Pregnancy typically divided into three trimesters is characterized by physiological changes which are reversible while Pathologic variations of these changes are are not, thus persisting even after pregnancy. A systolic blood pressure ≥160 or diastolic blood pressure ≥110 and/or proteinuria >5g in a 24-hour period is an indicative of severe preeclampsia (Arulkumaran,*et al.*, 2013).

Increased uric acid level is a key clinical feature of preeclampsia; higher levels correlate with significant maternal and fetal morbidity and mortality as recorded by researchers.Several researchers have

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developed interest in studying the relationship between serum uric acid level and pregnancy induced diseases like preeclampsia, hypertension etc. The role of uric acid in the pathogenesis of these pregnancy induced conditions like preeclampsia is characterized by hypertension, endothelial dysfunction and renal dysfunction. For some researchers, uric acid is not a consistent predictive factor for the development of pre-eclampsia but its levels generally increase once the disease manifests, and plasma levels of uric acid approximately correlate with disease severity.

Many tests aimed at predicting increased uric acid as a single biomarker of pre-eclampsia has been carriedoutbutthere still exist paucicity of information sufficient to predict pre-eclampsia disorders . According to some studies, serum uric acid lacks sensitivity and specificity as a diagnostic tool whereas another group of the researchers indicated uricemia as a predictor of pre-eclampsia in pregnant ladies. The present study was designed to assess whether SUA can be used as a biochemical indicator or not in pre-eclamptic patients (Pramanik*et al.*, 2012).This study is to evaluate and review the association between the serum levels of uric acid in normal and preeclamptic pregnancies per trimester , thereby broadening our knowledge in the contribution of hyperuricemia vascular damage in pre-eclampsia as compared to normal pregnancy.

Pregnancy typically divided into three trimesters has physiological changes. There are also pregnancy induced pathologic variations as well; some of these changes are reversible while others are not, thus persisting even after pregnancy. A systolic blood pressure ≥160 or diastolic blood pressure ≥110 and/or proteinuria >5g in a 24-hour period is also indicative of severe preeclampsia (Arulkumaran,*et al.*, 2013).

Increased SAU level is a key clinical feature of pre-eclampsia; higher levels correlate with significant maternal and fetal morbidity and mortality as recorded by researchers as a result several researchers have developed interest in studying the relationship between uric acid level and pregnancy induced diseases like preeclampsia, hypertension etc. The role of uric acid in the pathogenesis of these pregnancy induced conditions like preeclampsia is characterized by hypertension, endothelial dysfunction and renal dysfunction. For some researchers, uric acid is not a consistent predictive factor for the development of pre-eclampsia but its levels generally increase once the disease manifests, and plasma levels of uric acid approximately correlate with disease severity.

II. MATERIALS AND METHODS

Blood samples were collected from both normal pregnant and pre-eclamptic pregnant women, attending antenatal care in some selected primary health care centers, privates and general hospitals within Obio-Akpor Local Government Area Rivers State.

The studied population consisted of 200 pregnant women divided into 2 groups; group 1 comprises, 100 normal pregnant women while group 2 comprises of another 100 pre-eclamptic pregnant women. Preeclampsia is defined at a blood pressure of at least 140/90mmHg – 160/110mmHg on two occasion each 6hrs apart accompanied by proteinuria of at least 1+ - 3+++ on dip stick testing.

Collection of blood sample

Blood samples were collected from all subjects for serum uric acid test. They are collected by venal puncture, as cleanly as possible using sterile equipment.

Method of blood collection

New vacationer needle and vacationer lithium heparin bottle were used for each of the pregnant women.

The spotted area for the puncture was swabbed with 70% alcohol (methylated spirit).

The upper part (arm) of the spotted area (vein) was tied with a tourniquet.

In a vacutainer method, 5ml of the blood specimen was collected into vacutainer lithium heparin bottle.

The blood specimens were spun in a centrifuge at 3500rpm for 10mins, to separate the serum from the blood cells.

The serum specimens are decanted into a new fresh bottle without any anticoagulant and refrigerated for preserving purposes.

Measurement of blood pressure

All the subjects (i.e. the pregnant women both normal and pre-eclamptic) underwent a blood pressure measurement using manual method (i.e. with stethoscope, blood pressure cuff, mercury column sphygmomanometer) (Pickering, T. G *et al.*, 2005).

TheBlood pressure measurement was repeated for accuracy blood pressure was termed high when the systolic reading was from 140mmHg and above, and diastolic reading from 90mmHg and above.

Test for Protein In Urine.

Test of protein in urine was carriedoutby the method of colourchange. Protein was said to be present when the colour changed from light yellow (+) to green (+++), (30 – 500mg/dl) and negative when the colour remained dark yellow. The strip detect values above 10mg protein/dl urine.

Test For Serum Uric Acid.

The serum uric acid was done by enzymatic colorimetric method, using 721 visible spectrophotometer at the wavelength of 520nm. At this method the uricase transforms uric acid into allantoin with formation of hydrogen peroxide which, in presence of peroxidase (POD), reacts with 4-aminoantipyrine and 3-hydroxyl-2,4,6-triiodobenzoic acid to produce a coloured complex which intensity is directly proportional to the uric acid concentration in the sample. (Barham D., *et al.,* Analyst. 1972).

Body Mass Index Measurement (BMI).The BMI of each subject was determined by measuring the height (m), weight (Kg) and dividing the mass by the square of the height (**(kg/m^2)**.

III. STATISTICAL ANALYSIS

Where applicable, results were expressed as mean ± SD. Means were compared for statistical significant difference by one-tailed analysis of variance (ANOVA). Effects were considered significant at $P < 0.05$ in all cases.

Sample size determination.

Sample size (n) = $\dfrac{(u+v)^2\,[p_1(1-p_1) + p_2\,(1-p_2)]}{(p_1 - p_2)^2}$

Where n = minimum sample size.

u= one sided percentage point of the standard normal deviate corresponding to 100% (the power) i.e. 90%.

v= percentage point of the standard normal deviate corresponding to two sided significance level (5%).

p_1= prevalence of uric acid level in pre-eclampsia pregnancy.

p_2= prevalence of uric acid level in normal pregnancy.

IV. RESULTS

The results and comparisons of body mass index (BMI), blood pressure (BP), serum uric acid and protein in urine for group I (normal pregnancy) and group II (pre-eclampsia), in each of the three stages of pregnancy were presented in Tables 4.1, 4.2, 4.3 respectively, with P-value. Figures 4.1 – 4.4 shows the charts of body mass index (BMI) in all the trimesters, blood pressures (BP) in all the trimesters, serum uric acid in all the trimesters and protein in urine in all the trimesters respectively. All showing between group I (normal) and group II (pre-eclampsia). Values of $p > 0.05$ are considered not significant while values of $p < 0.05$ are considered significant.

Table 4.1: Results and comparison of body mass index (BMI), blood pressure (BP), serum uric acid and protein in urine, in 1st trimester, for normal and pre-eclamptic women.

Groups	No.	I (Normal pregnancy)	II (Pre-eclampsia)	P-value
Body mass index (kg/m^2)	200	23.4±3.0$^{(a)}$	23.1±1.4$^{(b)}$	a vs. b =P>0.05
Blood pressure (mm/Hg)	200	Systole: 118.5±1.9$^{(c)}$ Diastole: 75.4±3.9$^{(e)}$	Systole:143.2±2.9$^{(d)}$ Diastole: 92.5±3.9$^{(f)}$	c vs. d = P<0.05 e vs. f = P<0.05
Serum Uric acid (mg/dl)	200	3.5±0.1$^{(g)}$	7.2±1.1$^{(h)}$	g vs. h = P<0.05
Protein in Urine (mg/dl)	200	Nil (10.0)$^{(i)}$	119.6±129.8$^{(j)}$	i vs. j = P<0.001

Table 4.1 above shows the results and comparison of body mass index (BMI), blood pressure (BP), serum uric acid and protein in urine. The body mass index (BMI) of a normal person falls within the normal range of 18.5 – 24.9kg/m^2, whereas in the pre-eclamptic pregnancy during 1st trimester it was 23.1±1.4, falling within normal range. Blood pressure (BP) is normal at systole; 110 – 120mm/Hg and diastole; 70 – 80mm/Hg, but in pre-eclamptic, the blood pressure (BP) is very significant as it falls within 143.2±2.9 for systole and 92.5±3.9 for diastole. The serum uric acid of a normal person is 2.6 – 6.0mg/dl, whereas in pre-eclamptic

pregnancy, at 1st trimester, it was 7.2±1.1 with P<0.05. Protein cannot be detected in the urine of a normal person whereas in pre-eclamptic, it is detected from + (30mg/dl) - +++ (500mg/dl). In 1st trimester, the protein in urine for pre-eclamptic pregnancy was 119.6±129.8 as P<0.05.

Table 4.2: Results and comparison of body mass index (BMI), blood pressure (BP), serum uric acid and protein in urine, in 2nd trimester, for normal and pre-eclamptic women.

Groups	No.	I (Normal pregnancy)	II (Pre-eclampsia)	P-value
Body mass index (kg/m²)	200	23.9±0.2[a]	25.6±1.5[b]	a vs. b = P<0.05
Blood pressure (mm/Hg)	200	Systole: 117.6±1.7[c] Diastole: 73.1±0.7[e]	Systole: 145.7±3.7[d] Diastole: 93.4±4.1[f]	c vs. d = P<0.05 e vs. f = P<0.05
Serum Uric acid (mg/dl)	200	3.5±0.3[g]	7.7±0.8[h]	g vs. h = P<0.05
Protein in Urine (mg/dl)	200	Nil (10.0)[i]	177.1±129.4[j]	i vs. j = P<0.001

The body mass index (BMI) increases as the gestational age increases, in 2nd trimester it increases to 25.6±1.5kg/m² above the normal range making the P-value significant. There is also an increase in blood pressure (BP) to 145.7±3.7mm/Hg in systole and 93.4±4.1mm/Hg in diastole with P<0.05. Serum uric acid in pre-eclamptic pregnancy increases to 7.7±0.8mg/dl at 2nd trimester with a significant P-value. Protein was still detected at a higher rate of 177.1±129.4mg/dl in urine, P<0.05.

Table 4.3: Results and comparison of body mass index (BMI), blood pressure (BP), serum uric acid and protein in urine, in 3nd trimester, for normal and pre-eclamptic women.

Groups	No.	I (Normal pregnancy)	II (Pre-eclampsia)	P-value
Body mass index (kg/m²)	200	28.7±6.4[a]	29.9±1.1[b]	a vs. b = P>0.05
Blood pressure (mm/Hg)	200	Systole: 118.4±3.4[c] Diastole: 74.7±1.3[e]	Systole: 145.8±2.9[d] Diastole: 94.0±2.2[f]	c vs. d = P<0.05 e vs. f = P<0.05
Serum Uric acid (mg/dl)	200	3.7±0.2[g]	7.8±1.1[h]	g vs. h = P<0.05
Protein in Urine (mg/dl)	200	Nil (10.0)[i]	178.4±130.6[j]	i vs. j = P<0.001

At the final stage of the pregnancy (3rd trimester), it was noticed and recorded that there is still a very significant increase in the body mass index (BMI), as it is 29.9±1.1kg/m². Same as blood pressure (BP) with systolic rate at 145.8±2.9mm/Hg and diastolic rate at 94.0±2.2mm/Hg. Serum uric acid increased more to 7.8±1.1mg/dl and protein detected at 178.4±130.6mg/dl, all giving a result of P<0.05.

Discussion.

Findings of other researchers showed that elevated serum Uric acid concentration is a marker of oxidative stress tissue injury dysfunction and that it is an independent risk factors for cardiovascular disease (Johnson *et al*., 2003, Shi *et al*., 2003) ,giving rise to high blood pressure. During uncomplicated pregnancies, serum uric acid concentrations decrease by 25% - 35% in early pregnancy but increase throughout pregnancy until towards the end of pregnancy when the concentrations approach non- pregnancy levels (Lind *et al*., 1984). In this present study, we found an elevated serum uric acid level in the dysfunctioning pregnancies; this founding is corroborated with other reports (Cunningham *et al*., 2005, Kang *et al*., 2004). It was proposed that those pregnancy -mediated changes in serum uric acids are primarily the result of altered renal handling. Increased serum uric acid in pre-eclampsia are secondary to reduced renal urate clearance because of renal dysfunction (Conad*et al*., 1999) and also were due to increased xanthine oxidase activity (Many *et al*., 1996).

Increased serum uric acid level is a key clinical feature of pre-eclampsia; higher levels correlate with significant maternal and fetal morbidity and mortality. The cause of hyper-uricemia and its specific role in the pathogenesis of pre-eclampsia, however, remains unclear. Nevertheless, there have been recent data supporting a pathogenic role potentially in the hypertension and endothelial cell dysfunction of pre-eclampsia (Lam *et al*., 2006). It is also possible that increased serum uric acid value may indicate the presence of undiagnosed sub - clinical renal disease in some subjects and this might increase the risk for pre-eclampsia. Increase in serum uric

acid may be the result of not only changes in glomerular filtration rate (GFR) but also proximal tubular function and secretion and synthesis by xanthine oxidase (Powers *et al*., 2006).

As seen in this study, an increase in serum uric acid causes increase in blood pressure (BP) and increased excretion of protein in the urine (proteinuria). It is also noted that serum uric acid increases as the pregnancy gets old. This gives rise to pre-eclampsia usually occurring after 32weeks; however if it occurs earlier, it is associated with worse outcomes (Arulkumaran& Lighthouse 2013).

Pre-eclampsia affecting approximately 2 – 8 % of all pregnancies worldwide (Eiland 2012; Al – Jameil*et al*., WHO 2005) are with onset of symptoms in the late second or third trimester, most commonly after the 32nd week. Other studies have reported that women with pre-eclampsia and hyperuricemia have a more severe form of pre-eclampsia with an increased risk for preterm and small gestational age births (Fadel*et al*., 1976, D'Anna*et al*., 2000, Wakwe*et al*., 1999). A study by Mazalli*et al* (2001), demonstrated that inhibiting the activity of uricase in a rat model led to the development of hypertension and renal injury; these changes were mediated by the stimulation of the renin angiotensin system.

In conclusion, We have observed that increase in serum uric acid is not significant to body mass index (BMI),but very significant to blood pressure (BP) and proteinuria, which are the major causes of pre-eclampsia in pregnancy. Thus increase in serum uric acid can be related to pre-eclampsia, and can be used as a marker for pre-eclampsia. Adequate screenings, monitoring and routine check-up during pregnancy may prevent hyperuricemia, thereby controlling the rate of pre-eclamptic women, maternal and fetal morbidity and mortality. However, further studies on a larger population can still be undertaken to validate its sensitivity and specificity

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